

Lung Cancer Etiology and Genetics

Neil Caporaso

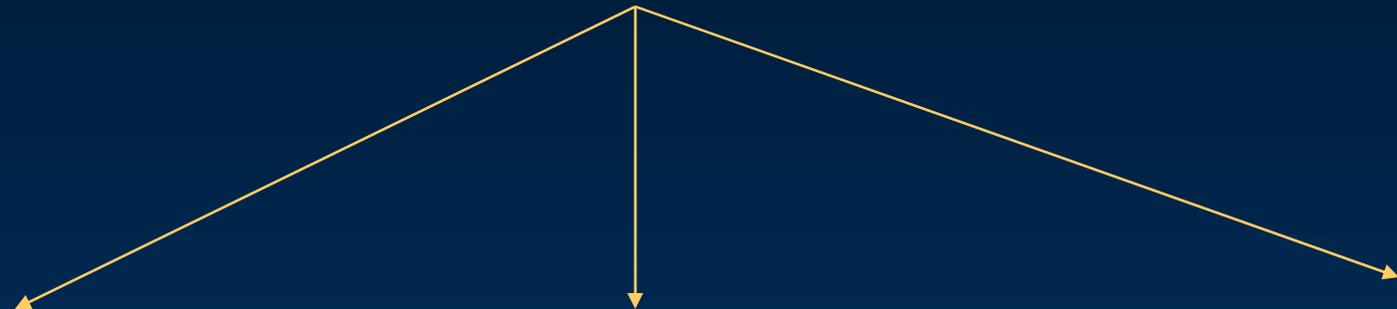
Division of Cancer Etiology and Genetics

June 11, 2009

A personal journey in the NCI intramural program.....

Goal to identify hereditary component of lung cancer

3 lines of evidence available in the late 1980's

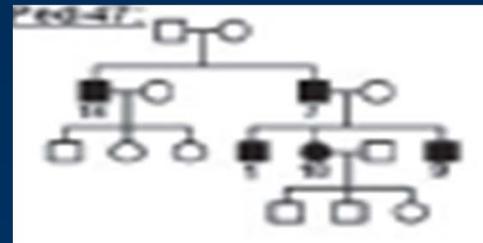


Family History
Lung Cancer

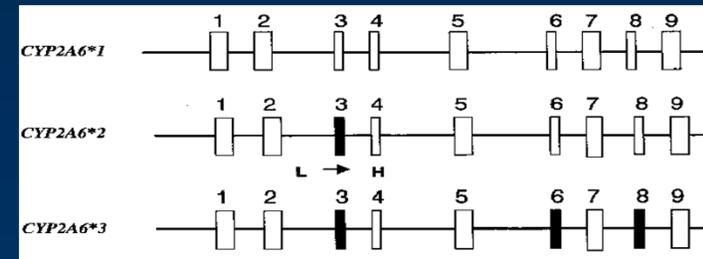
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Tokuhata and Lilienfeld 1983

Pedigrees



Pharmacogenetics



A Population Perspective on Lung Cancer and Smoking

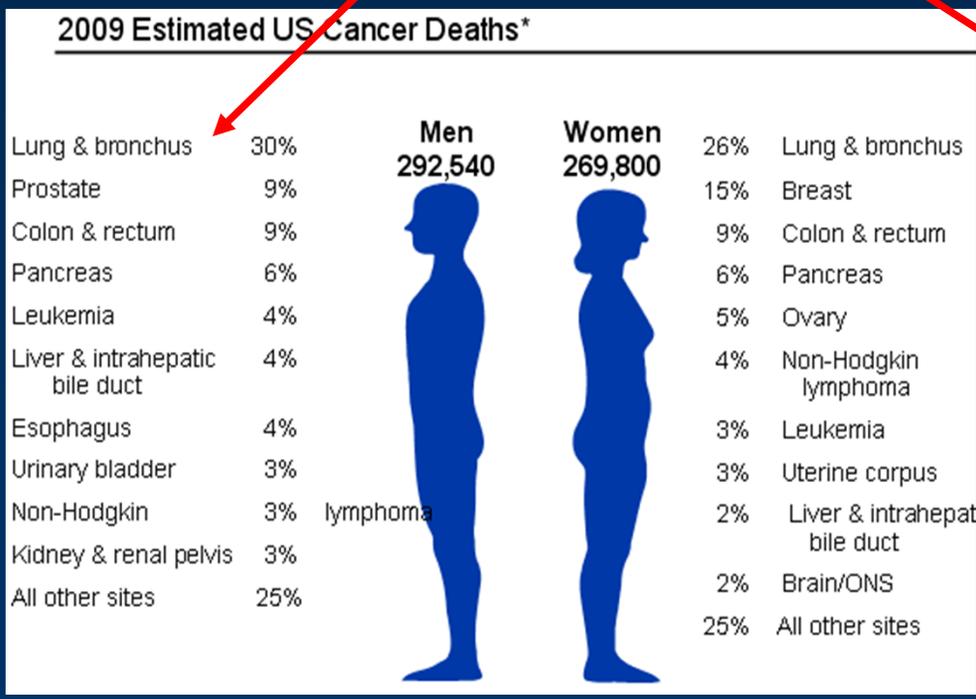
- Descriptive Epidemiology
- Molecular Epidemiology
- Integrative Epidemiology
- Genomics
 - Smoking
 - Lung Cancer
- Importance of Key Subgroups
- Summary

A Population Perspective on Lung Cancer and Smoking

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The lung cancer challenge....

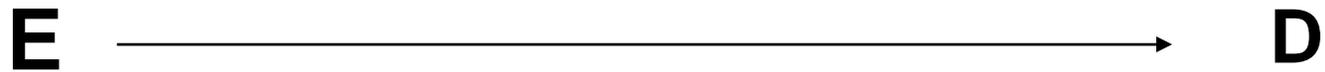
- 1- Drives overall cancer mortality in the US and worldwide
- 2- Treatment and screening pose challenges
- 3- Lung cancer is paradigm for genetics of complex disease
- 4- Clearest example of environment and gene in cancer
- 5- The clearest example of a genetically influenced behavior associated with the leading public health problem in the world



Trends in Five-year Relative Survival (%)* Rates, US, 1975-2004

Site	1975-1977	1984-1986	1996-2004
All sites	50	54	66
Breast (female)	75	79	89
Colon	52	59	65
Leukemia	35	42	51
Lung and bronchus	13	13	16
Melanoma	82	87	92
Non-Hodgkin lymphoma	48	53	65
Ovary	37	40	46
Pancreas	3	3	5
Prostate	69	76	99
Rectum	49	57	67
Urinary bladder	74	78	81

Traditional epidemiology



Exposure

Disease

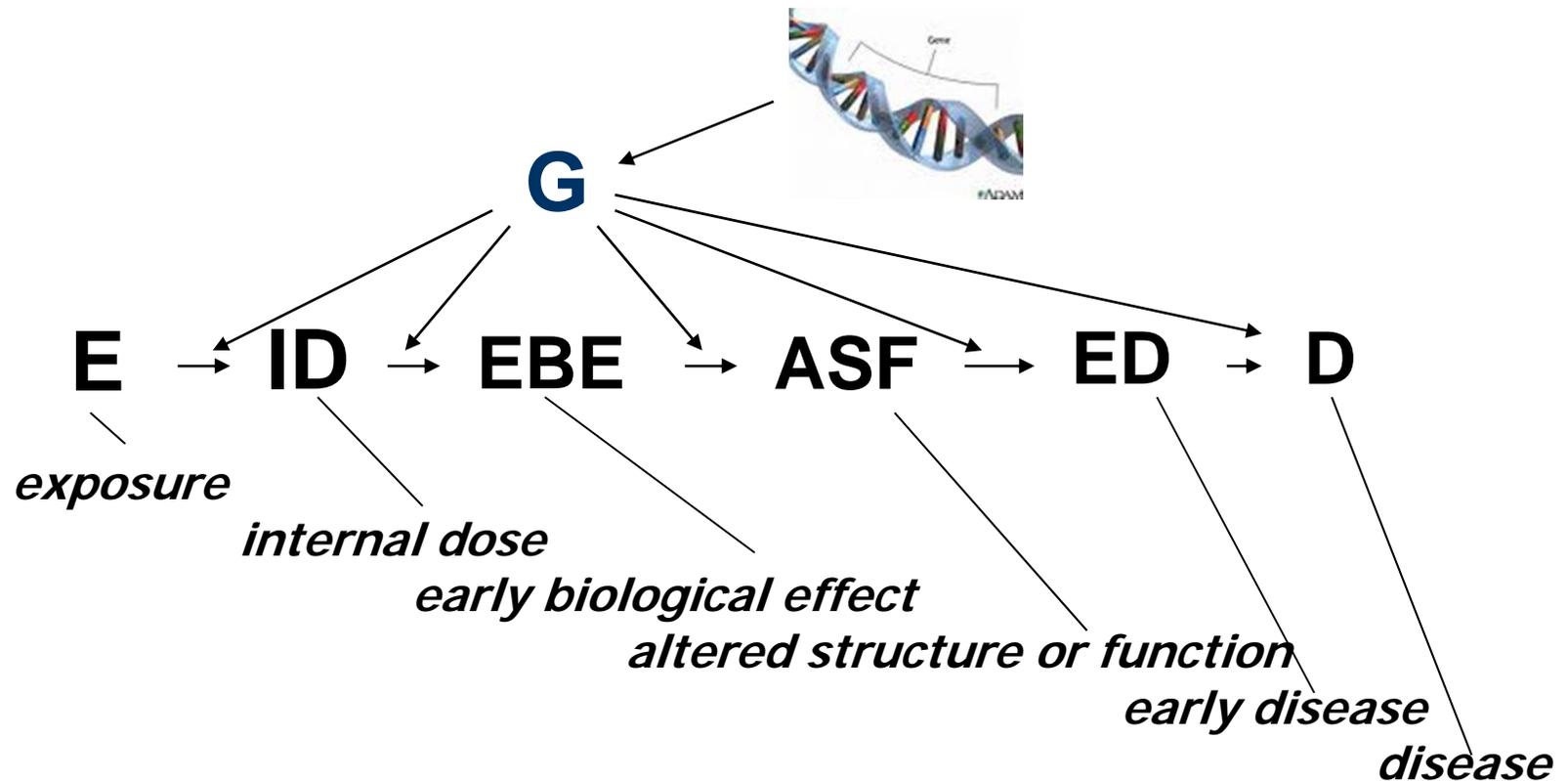
Tobacco



Lung Cancer



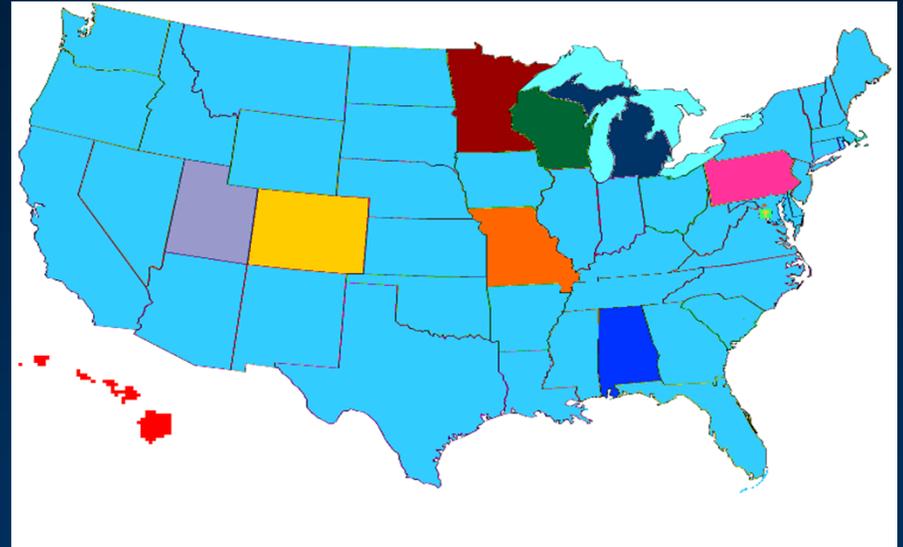
Molecular epidemiology



Adding biomarkers allows us to investigate genes and mechanisms

PLCO Trial: Study Design

- Screening Centers: 10
- Coordinating Center
- Participants: 154,935
- Gender: 50:50
- Age: 55-74 years
- Recruitment: 1993-2001
- Screening: 1993-2006
- Baseline questionnaire
- Dietary questionnaires
- Follow-up:
 - Annual surveys
 - Monitoring and QA
 - Mortality searches
 - Interim analyses regularly
- 847 lung cancer cases and 847 controls participate in GWAS



<http://prevention.cancer.gov/programs-resources/groups/ed/programs/plco>

EAGLE (Environment and Genetics in Lung Cancer Etiology)

National Cancer Institute U.S. National Institutes of Health | www.cancer.gov

EAGLE

Environment And Genetics in Lung cancer Etiology

Contact Us

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Dictionary

Smoking is the leading cause of preventable morbidity and mortality. Lung cancer is the major cause of cancer death in the developed world. No prevention, screening or therapeutic regimen has been proven to be effective against lung cancer. New approaches are urgently needed.

EAGLE is a unique collaboration between the United States (NCI) and Italy (UNIM). It represents collaborative efforts of over 100 scientists, clinicians and support staff. The study goals are to identify the genetic and environmental determinants of both lung cancer and smoking and to shed light on the determinants of therapy success and long term survival in patients diagnosed with lung cancer. The **EAGLE** group has completed data collection for a multi-center case-control study of lung cancer in the Lombardy Region of Italy, over 2000 cases and 2000 controls were enrolled between 2002 and 2005.

The rich integrative platform of **EAGLE** will enable a new generation of scientists to address the scientific and clinical challenges posed by lung cancer.

EAGLE Principal Investigators:
Maria Teresa Landi, MD, PhD
Neil Caporaso, MD
Genetic Epidemiology Branch, DCEG
National Cancer Institute, NIH

Scenes from the EAGLE Study

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DCEG NCI FIRSTGOV

BMC Public Health



Study protocol

Open Access

Environment And Genetics in Lung cancer Etiology (EAGLE) study: An integrative population-based case-control study of lung cancer

Maria Teresa Landi*¹, Dario Consonni², Melissa Rotunno¹,
Andrew W Bergen¹, Alisa M Goldstein¹, Jay H Lubin¹, Lynn Goldin¹,
Michael Alavanja¹, Glen Morgan³, Amy F Subar³, Ilona Linnoila⁴,
Fabrizio Previdi², Massimo Corno², Maurizia Rubagotti², Barbara Marinelli²,
Benedetta Albetti², Antonio Colombi², Margaret Tucker¹,
Sholom Wacholder¹, Angela C Pesatori^{†2}, Neil E Caporaso^{†1} and Pier
Alberto Bertazzi^{†2}

Example from EAGLE: molecular epidemiology approach

Epidemiology 'doneness module'

Biospecimens

3.05 ► Se Lei mangia i seguenti tipi di carne, che grado di cottura hanno usualmente?

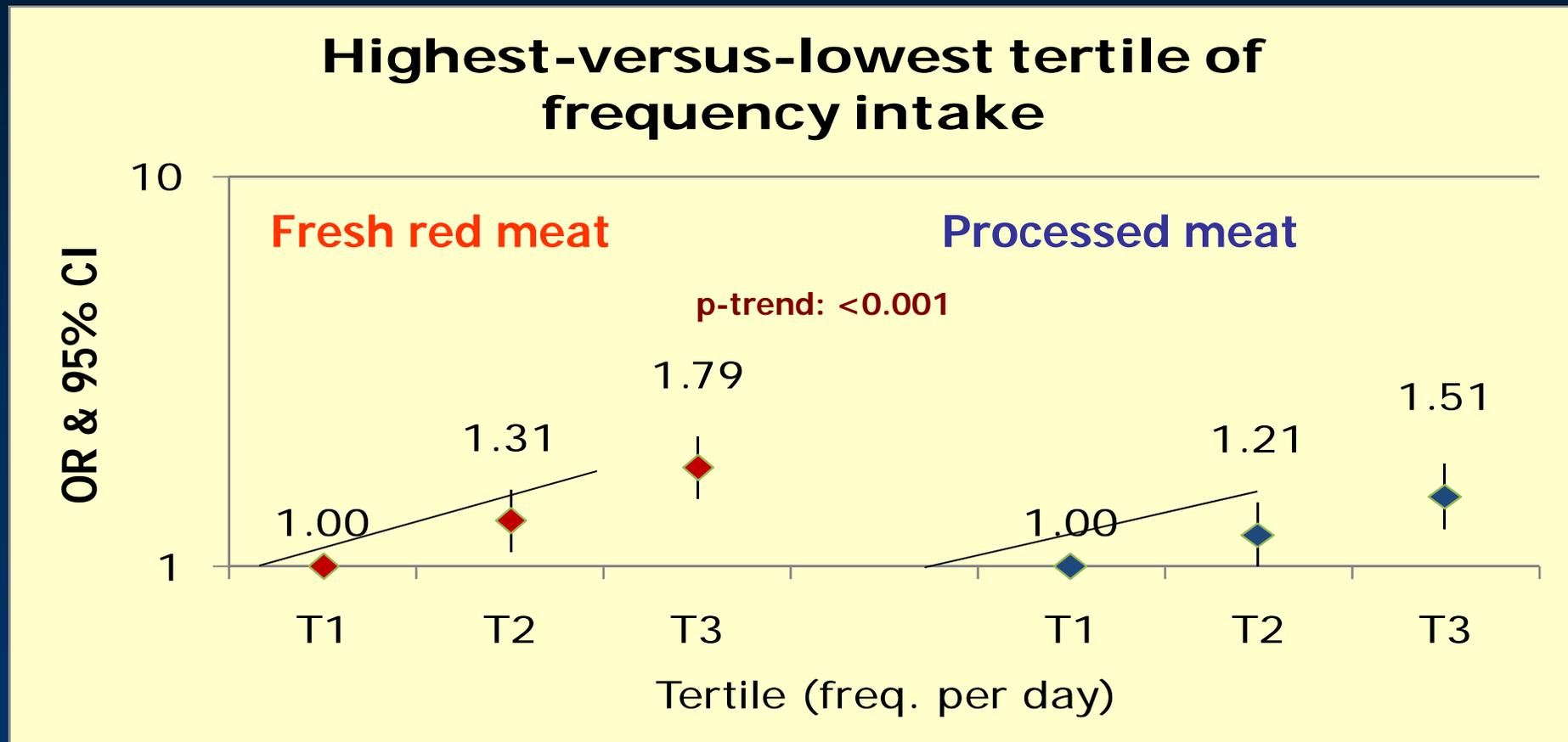
Tipi di carne	Ben cotte (cotte dentro)	Media (rosa dentro)	Al sangue (rosse dentro)
1. BISTECCA DI MANZO	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. HAMBURGER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. BRACIOLA DI MAIALE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. BRACIOLA O COSTOLETTA DI VITELLO	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. POLLO	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3.06 ► Se Lei mangia i seguenti tipi di carne, che grado di bruciatura hanno di solito?
Per favore faccia riferimento ai seguenti quattro gruppi composti ciascuno da tre foto, per indicare il grado di bruciatura di tutte le carni listate qui sotto.

1. Bistecca di Manzo



Higher frequency of fresh red and processed meat intake **increased** lung cancer risks



Lam et al, 2009, Cancer Res.

A Population Perspective on Lung Cancer and Smoking

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National Cancer Institute U.S. National Institutes of Health | www.cancer.gov

EAGLE

Environment And Genetics In Lung cancer Etiology

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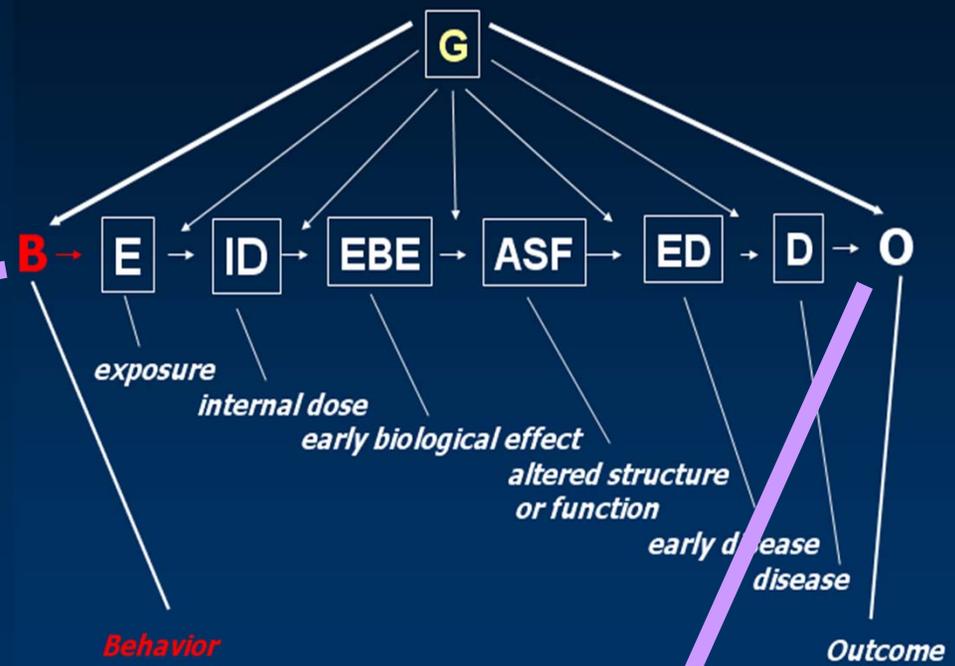
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DCEG NCI UNIMI NIH FIRSTGOV

Integrative epidemiology



Instruments

- Fagerstrom Nicotine Dependency
- DSM-IV Nicotine Dependency
- Hospital Anxiety and Depression Scale
- Eysenck Personality Inventory
- CESD- Depression
- Attention Deficit Inventory
- Attitudes and Knowledge about Smoking
- Intention to Quit Smoking

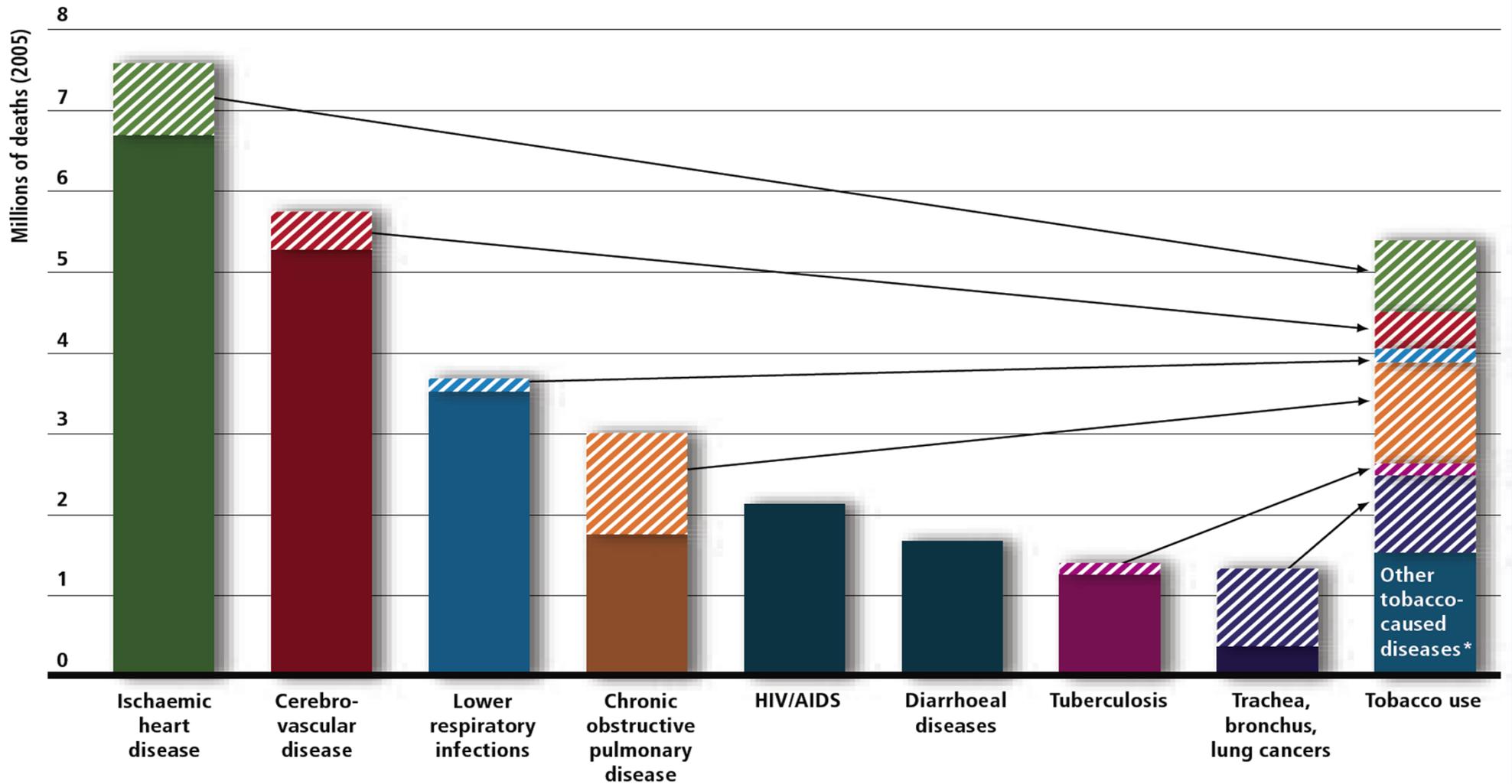


Treatment
 Survival
 Prognostic and Clinical

A Population Perspective on Lung Cancer and Smoking

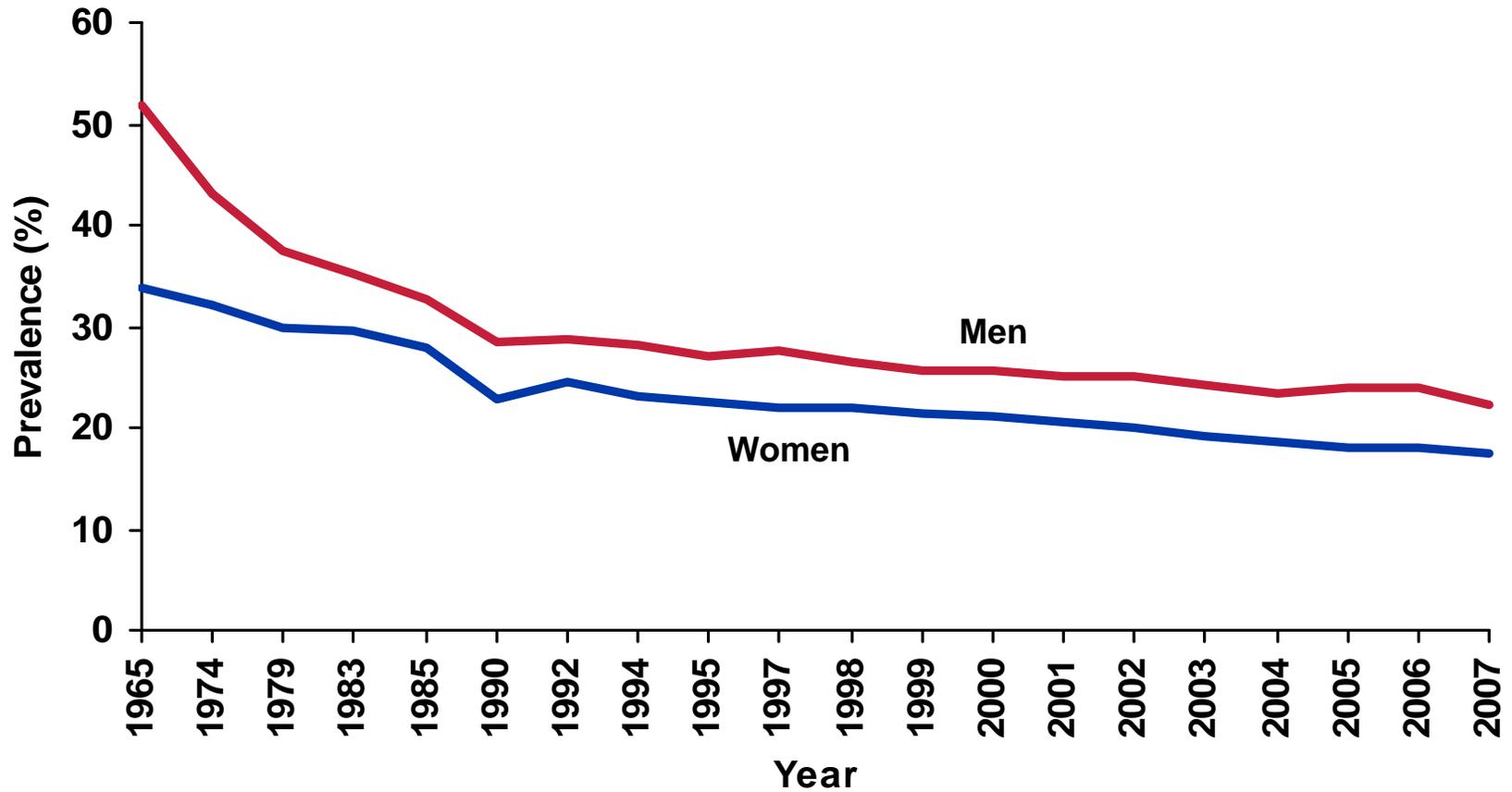
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Tobacco Is a Risk Factor for 6 of the World's 8 Leading Causes of Death



Hatched areas indicate proportions of deaths related to tobacco use.

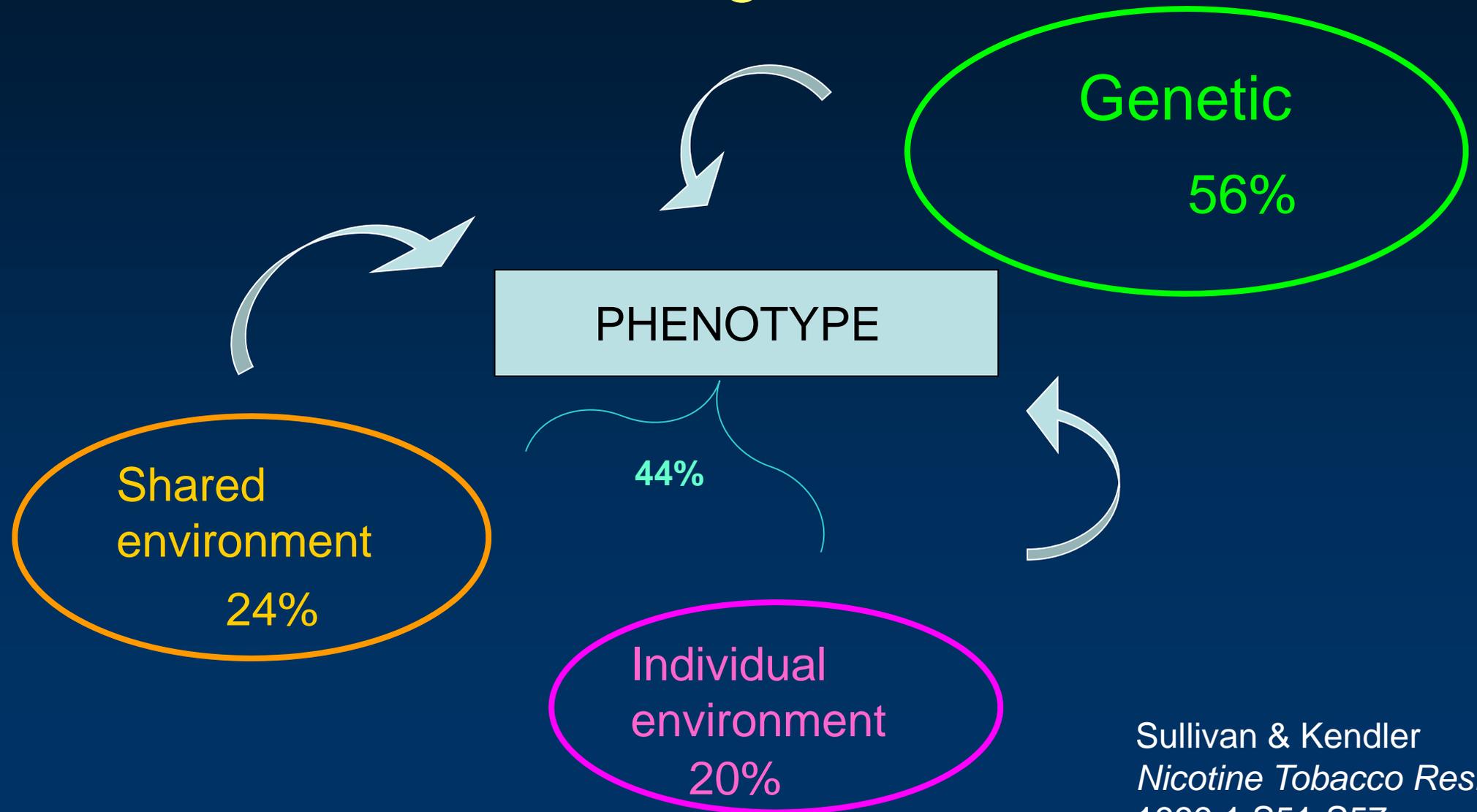
Trends in Cigarette Smoking Prevalence* (%), by Sex, Adults 18 and Older, US, 1965-2007



*Redesign of survey in 1997 may affect trends.

Source: National Health Interview Survey, 1965-2007, National Center for Health Statistics, Centers for Disease Control and Prevention, 2008.

Strong and consistent evidence for a genetic contribution to smoking from twin studies...



Sullivan & Kendler
Nicotine Tobacco Res.
1999;1:S51-S57

Smoking GWAS, 2 cohort studies

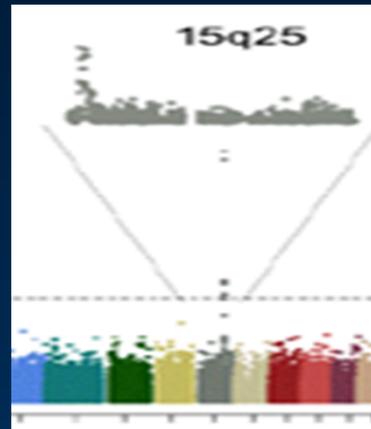
Prostate, Lung, Colon Ovary
2,289 male, Caucasian

Nurses Health Professional
Study (NHS)
2,282 female, Caucasian

Illumina HumanHap 550K

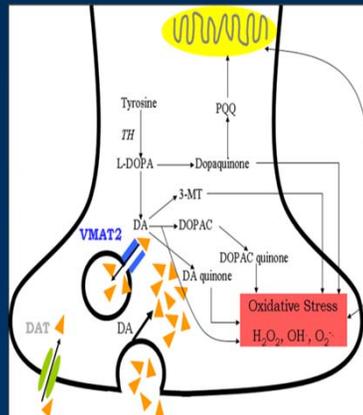


2 loci are prominent....



Nicotinic receptor
Evidence:
very strong

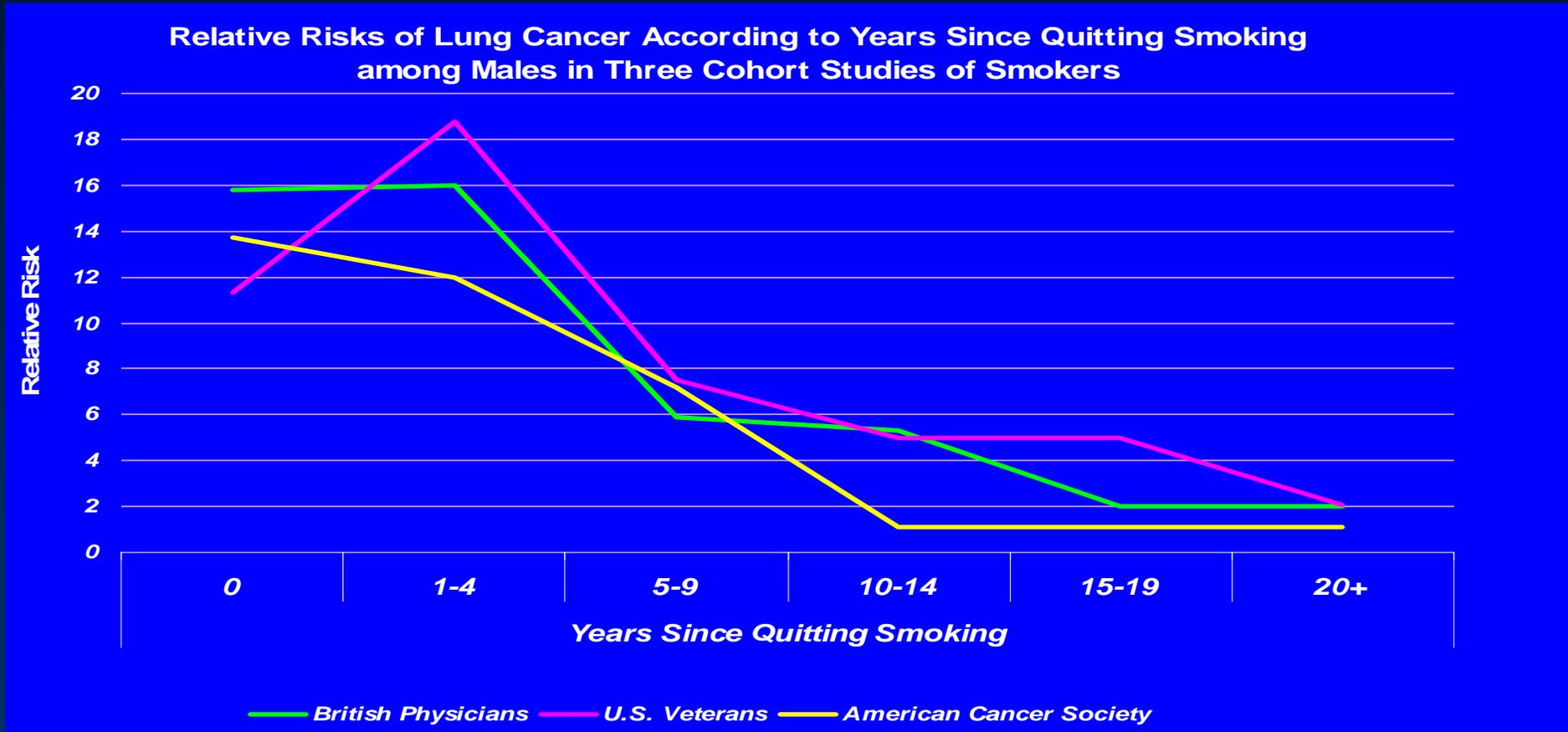
—————> Varenicline (*Chantix*)



Dopamine pathway
Evidence:
requires confirmation

—————> Bupropion

Lung cancer rate drops after smoking cessation but...



....currently most lung cancer in the United States is diagnosed in former smokers!!!

Lung Cancer GWAS

	N. SUBJECTS		LOC	DESIGN	CHIP
	Cases	Controls			
NCI Studies					
EAGLE	1,920	1,979	Italy	Pop c/c	550
ATBC	1,732	1,271	Finland	Cohort	610/550
PLCO	1,390	1,924	USA	Cohort	550/610/317+240S
CPS-II	697	674	USA	Cohort	610/1M/550
NCI TOTAL	5,739	5,848			
Meta-analysis					
UK	1,987	1,438	ICR Sut	Hosp cases Birth cohort cont	550
Central Europe	1,837	1,438	East Eur	MC c/c	300-370duo
Texas	1,154	1,137	USA	Hosp c/c	317
Iceland	719	6,030	Iceland	Pop c/c	550
HCF Germany	506	480	Germany	Pop c/c, age<50	550
CARET	397	393	USA	Clin Trial	370duo
HUNT2/Tromso	394	382	Norway	Hosp c/c	370duo
Canada	332	505	Toronto	c/c	317
France	135	146	Paris+	Hosp c/c	317
Estonia	109	875	Estonia	hosp c/c	317/370duo
META TOTAL	7,561	13,818			
GRAND TOTAL	13,300	19,666			

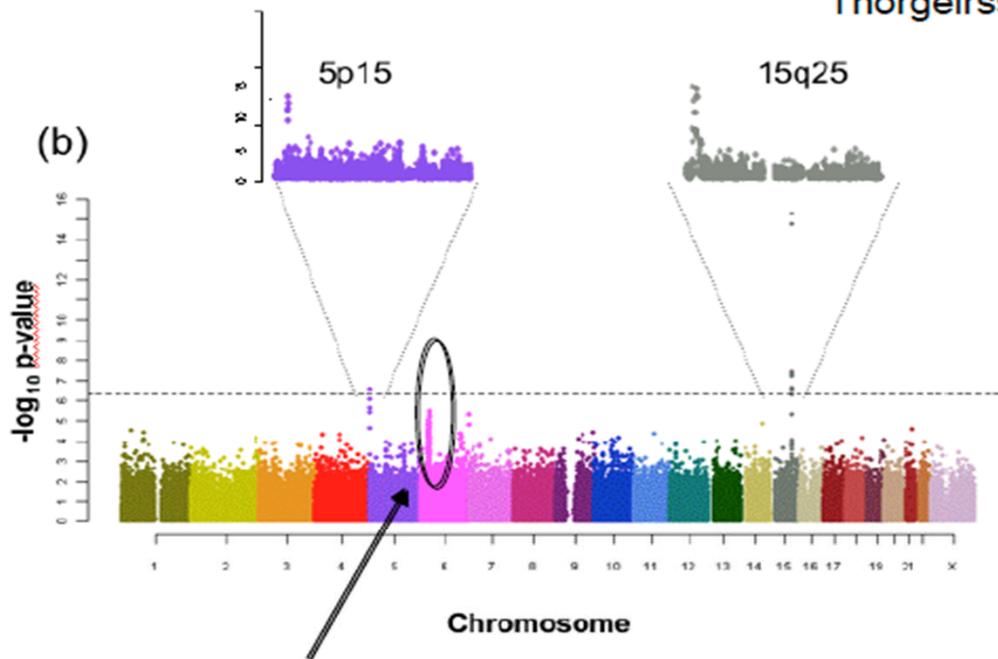
Lung and Smoking GWAS to date

- Three implicated loci on chromosome 5, 6 and 15.
- Chr15q25 (nicotinic receptor) implicated in smoking

McKay et al. Nat Genet. Dec 2008
Chr5p15: 2 loci in *TERT* and *CPTM1L*

Amos et al. Nat. Genet. April 2008
Hung et al. Nature. Apr 2008
Thorgeirsson et al. Nature. April 2008

Chr15q25: nicotinic acetylcholine receptor genes (*CHRNA5*, *CHRNA3*)



Selected variants:

			Caucasian	Asian
chr15q25	<i>CHRNA5</i>	rs16969968	X	X
	<i>Loc123688</i>	rs8034191	X	X
	<i>CHRNA3</i>	rs12914385		X
	<i>CHRNA3</i>	rs1317286		X
	<i>Loc123688</i>	rs931794		X
chr5p15	<i>TERT</i>	rs402710	X	X
	<i>CLPTM1L</i>	rs2736100	X	X
chr6p	<i>HLA</i>	rs2256543	X	
		rs4324798	X	

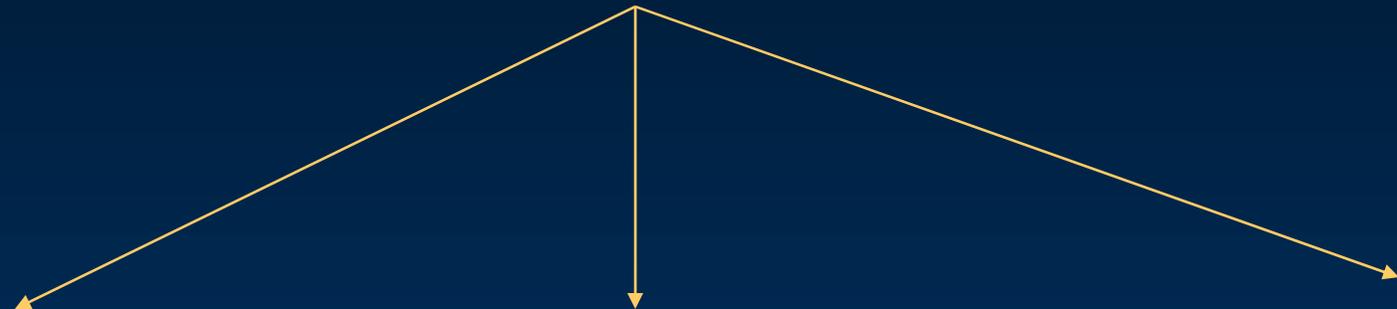
Hung et al. Nature. Apr 2008
Wang et al. Nat Genet. Dec 2008

Chr6p21: region of about 1Mb containing HLA genes

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Goal to identify hereditary component of lung cancer

3 lines of evidence available in the late 1980's

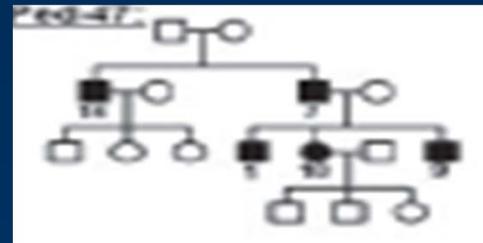


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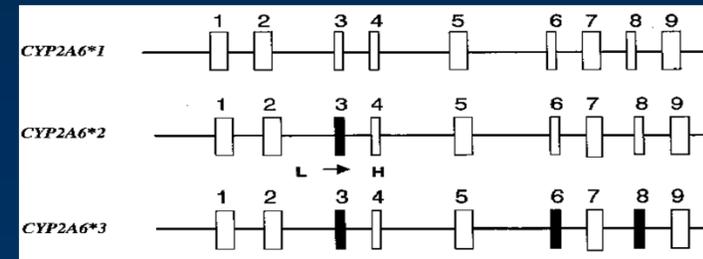
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Tokuhata and Lilienfeld 1963

Pedigrees



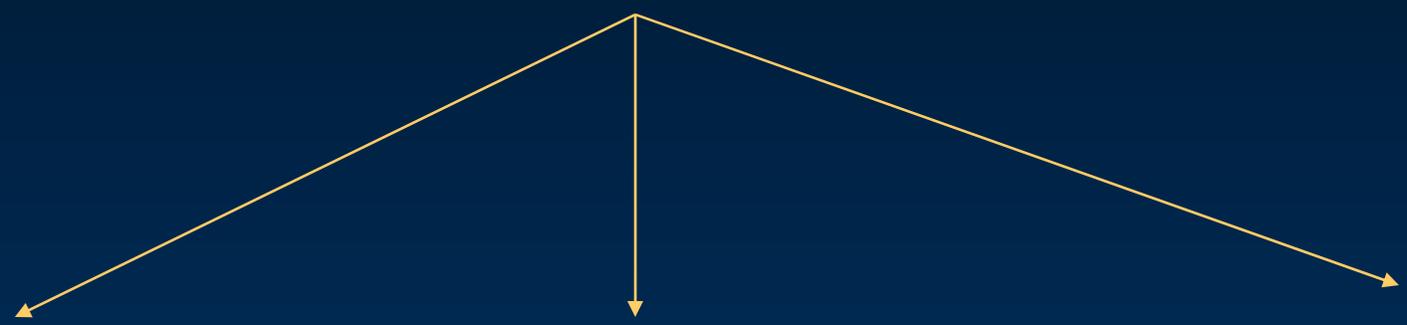
Pharmacogenetics



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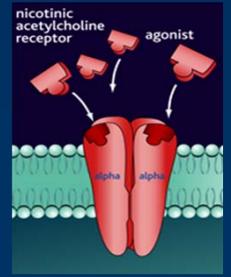
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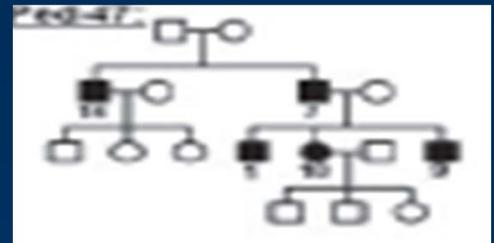
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Tokuhashi and Lilenfeld 1963



Amos et al. 2008

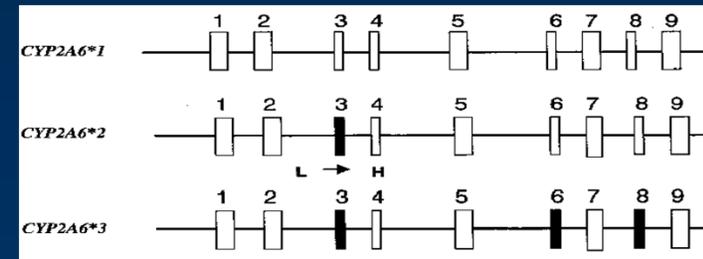
Pedigrees



Linkage studies

Bailey-Wilson et al, 2004

Pharmacogenetics



Pharmacogenomics

Caporaso et al, 2008

Sustained effort in the intramural program over time led to breakthroughs.....

80's

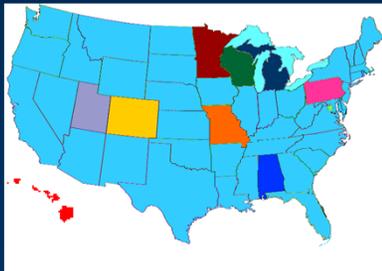
90's

00

KEY ADVANCES

case-control studies

PLCO



EAGLE



molecular epidemiology
larger studies
integrative epidemiology
technology
consortia efforts



Priorities from Population Perspective:

1. Genomics of Lung Cancer/Smoking

2. Genomics of Outcome

3. Key subgroup: African Americans

4. Key subgroup: Non- smokers

